APPENDIX 1

MEDICAL AFFAIRS Date: 22 NOV 1995
Report #: MR95312
Protocol # TOPMAT-EPPD-001

AN OPEN-LABEL, SINGLE-CENTER, SAFETY, PHARMACOKINETIC, AND EFFICACY STUDY OF TOPIRAMATE (RWJ-17021-000) ADJUNCTIVE THERAPY IN PEDIATRIC SUBJECTS WITH EPILEPSY

SYNOPSIS

PRINCIPAL INVESTIGATOR:
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STUDY DATES:
14 September 1994 - 23 May 1995

OBJECTIVES:
The objective of this study was to assess the pharmacokinetic and safety profile of topiramate as adjunctive therapy in pediatric subjects with epilepsy.

STUDY DESIGN:
This was an open-label, add-on, single-center study designed to evaluate the pharmacokinetic and safety profile of topiramate in pediatric subjects with epilepsy. Additionally, seizure counts were recorded. Eighteen subjects were enrolled and stratified according to age. Six subjects from each of the following age groups were enrolled: 4 - 7 years, 8 - 11 years, and 12 - 17 years. A subject's age was defined as his/her age at the baseline visit (Visit 1).

There were three phases to this study, a baseline phase, a treatment phase (in which the topiramate dosage was titrated and its pharmacokinetic profile was assessed), and a long-term extension phase. Only data collected from the baseline and treatment phases of the study are summarized in this report.

At Visit 1, subjects meeting the inclusion/exclusion criteria signed (or their parents/guardians signed) an Informed Consent form and entered a two-week baseline phase. During these two weeks, subjects were stabilized in a background antiepileptic drug (AED) regimen and were evaluated for study qualification.

At the first titration visit (Visit 2; Day 1) each subject received topiramate 1 mg/kg/day for one week. Thereafter, the titration schedule was as follows:

Visit 3 (Day 8):	After obtaining blood samples for the pharmacokinetic profile, increased topiramate from 1 mg/kg/day to 3 mg/kg/day
Visit 4 (Day 15):	After obtaining blood samples for the pharmacokinetic profile, increased topiramate from 3 mg/kg/day to 6 mg/kg/day
Visit 5 (Day 22)	Increased topiramate from 6 mg/kg/day to 9 mg/kg/day

Visits occurred weekly during this time. However, titration intervals could have been extended based on the needs of individual subjects. In addition, if a subject could not tolerate a dose, an adjustment could have been made by decreasing study medication to a maximum tolerated dosage. Subjects who could not tolerate the higher doses (e.g., 9 mg/kg/day), had the last plasma sample collected after at least seven days at their maximum tolerated dosage.

Subjects were maintained on each dosage for at least one week. During the interval between titration visits, topiramate was administered every 12 hours with dosing times each day not deviating by more than ± 1.0 hour. The maximum daily dose of topiramate during the treatment phase did not exceed 9 mg/kg/day or 800 mg/day, whichever was less. When calculating the amount of topiramate to be administered, the dosage was rounded to the nearest tablet strength. Only whole tablets were administered.

The following plasma and whole blood topiramate pharmacokinetic parameters were estimated for each subject: peak concentration (C_{max}); time to peak concentration (t_{max}); area under the concentration-time curve ($AUC_{0-\tau}$), as measured by the trapezoidal rule; and oral clearance (CL/F), as determined by dose/$AUC_{0-\tau}$

In addition, C_{max} and $AUC_{0-\tau}$ values were dose- and weight-normalized, and CL/F values were weight-normalized. C_{max} values were normalized to a 400 mg daily dose (400 mg dose for q24h regimen, 200 mg dose for q12h regimen) and a 70 kg body weight. $AUC_{0-\tau}$ values were normalized to a 200 mg dose and a 70 kg body weight. CL/F values were normalized to a 70 kg body weight.

The schedule of key study procedures is presented in Table 1. Data regarding seizure type and frequency were obtained from seizure diaries maintained by each subject (or guardian) for the duration of the baseline and treatment phase of the study. Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign measurements, physical examinations, and neurologic examinations.

Table 1: Schedule of Key Study Procedures for the Baseline and Treatment Phases (Protocol TOPMAT-EPPD-001)

Event	Visit 1 (Week -2) (Day -14)	Visit 2 (Week 0) (Day 1)	Visit 3 (Week 1) (Day 8)	Visit 4 (Week 2) (Day 15)	Visit 5 (Week 3) (Day 22)	Visit 6 (Week 4) (Day 29)	Final Visit[1]
Topiramate Administration		X	X	X	X	X	
Pharmacokinetic Assessments							
Topiramate Plasma Concentration		X					
Topiramate Pharmacokinetic Profile			X	X		X	
AED Plasma Concentration	X	X	X[2]	X[2]	X[2]	X[2]	X[2]
Seizure Counts							
Dispense Seizure Diary	X	X	X	X	X	X	
Collect/Review Seizure Diary		X	X	X	X	X	X
Safety Assessments							
Monitor Adverse Events			X	X	X	X	X[3]
Clinical Laboratory Tests	X		X			X	X[3]
Vital Sign Measurements	X	X	X	X	X	X	X
Neurologic Examination	X	X		X		X	
Physical Examination	X	X		X		X	X
Medical History	X	X[4]					

[1] The final visit was to occur the day after the last topiramate dose was taken for those subjects who prematurely withdrew from the study.
[2] Was scheduled at the investigator's discretion.
[3] Performed at seven-day follow-up visit if adverse events or abnormal laboratory test persisted at Final Visit.
[4] Updata medical history to capture any adverse events that occurred during baseline period.

NOTE: Interval from Visit 1 to Visit2 represents the Baseline Phase; Visit 2 through Visit 6 represents the Treatment Phase.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Eighteen subjects (six subjects within each age group) were enrolled in the baseline phase of this single-center study. Demographic and baseline characteristics are summarized in Table 2. Thirteen of the subjects were male and five were female. Valproic acid and gabapentin were the most frequently used background AEDs. The types of seizures experienced during the baseline phase by subjects enrolled in the study were generally similar among the age groups. Subjects experienced one or more seizure types including simple partial onset seizures (3 subjects), complex partial onset seizures (8 subjects), partial onset seizures evolving to secondarily generalized seizures (5 subjects), atonic seizures (4 subjects), and myoclonic seizures (3 subjects). One subject was seizure-free during the baseline phase. The median baseline monthly seizure rates

for the 4 to 7 and 12 to 17 year age groups were comparable while that for the 8 to 11 year age group was higher.

Table 2: Demographic and Baseline Characteristics (All Subjects; Protocol TOPMAT-EPPD-001)

Attribute	Age (yr) Group 4-7 (N=6)	8-11 (N=6)	12-17 (N=6)	Total (N=18)
Age (yr)				
Mean	5.5	9.7	15.0	10.1
SD	1.05	1.21	1.90	4.22
Gender				
% Male/Female	100/0	67/33	50/50	72/28
Weight (kg)				
Mean	20.1	33.8	64.6	39.5
SD	3.46	6.11	30.77	25.70
Baseline Average Monthly Seizure Rate[a]				
Mean	128.6	265.4	259.8	217.9
SD	133.71	361.68	332.06	283.54
Median	94.6	158.2	94.2	94.6
Range	9.3-382.0	0.0-936.0	4.0-730.3	0.0-936.0

[a] Monthly seizure rate = (number of seizures during baseline phase/total number of days in baseline phase) x 28.

DISCONTINUATION/COMPLETION INFORMATION:
None of the 18 subjects who met the screening criteria and entered the baseline phase discontinued prematurely from the treatment phase of the study.

PHARMACOKINETIC RESULTS:
The results from this study indicate topiramate pharmacokinetics were linear in 4 to 17 year-old pediatric subjects. Topiramate oral plasma clearance (CL/F) was independent of dose and steady-state plasma concentrations increased in proportion to dose (Table 3).

Table 3: Mean (SD) Steady-State Plasma Topiramate Pharmacokinetic Parameters (All Subjects, Protocol TOPMAT-EPPD-001)

	4 - 7 (q12h Dosing Unless Indicated Otherwise)			8 - 11 (q12h Dosing Unless Indicated Otherwise)			12 - 17 (q12h Dosing)		
Parameter	Target[a] Dose 1 mg/kg (N=6)	Target Dose 3 mg/kg (N=6)	Target[b] Dose 9 mg/kg (N=5)	Target Dose 1 mg/kg (N=5)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)	Target Dose 1 mg/kg (N=6)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)
C_{max} (µg/mL)	2.32 (0.64)	3.91 (2.16)	10.55 (1.91)	2.74[c] (0.77)	4.29 (1.49)	11.50 (3.13)	1.72 (0.68)	5.28 (2.47)	12.37 (4.61)
t_{max} (h)	1.8 (1.2)	1.2 (0.5)	1.0 (0.7)	0.8[c] (0.4)	2.8 (2.2)	2.2 (1.6)	1.0 (0.6)	1.1 (0.7)	1.8 (1.2)
$AUC_{0-\tau}$ (µg·h/mL)	23.5 (9.1)	30.7 (18.9)	78.5 (29.5)	21.2[d] (8.2)	40.7 (16.2)	102.7 (34.8)	14.7 (8.6)	48.2 (30.0)	111.1 (54.8)
CL/F (mL/min)	19.5 (5.6)	18.8 (6.4)	22.0 (7.2)	22.2[d] (8.6)	23.4 (9.0)	25.0 (8.1)	48.3 (33.6)	47.3 (33.1)	50.1 (34.7)

[a] q24h topiramate therapy.
[b] Data from Subject 13 excluded from analysis as outlier data.
[c] N = 2 for C_{max} and t_{max} - includes only q12h topiramate-treated subjects.
[d] N = 5 for $AUC_{0-\tau}$ and CL/F (all subjects, excluding Subject 4). Subject 4 data excluded from analysis because subject received an additional dose during the sampling interval.

Weight-normalized topiramate CL/F was higher in subjects receiving enzyme inducing concomitant antiepileptic drugs (mean = 70.1 mL/min/70 kg) when compared to subjects not receiving enzyme inducing concomitant antiepileptic drugs (mean = 33.1 mL/min/70 kg) (Table 4).

Table 4: Mean (SD) Dose- and Weight-Normalized Steady-State Topiramate Plasma Pharmacokinetic Parameters (All Subjects by Concomitant AED [With/Without Enzyme Inducers], Protocol TOPMAT-EPPD-001)

	Subjects With Concomitant Enzyme Inducers			Subjects Without Concomitant Enzyme Inducers		
Parameter	Target Dose 1 mg/kg (N=11)	Target Dose 3 mg/kg (N=11)	Target[b] Dose 9 mg/kg (N=10)	Target Dose 1 mg/kg (N=5)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)
C_{max} (µg/mL/400 mg Daily Dose and 70 kg)	7.89[a] (1.98)	6.73 (1.81)	6.39 (0.97)	13.98[c] (1.67)	11.65 (2.78)	10.17 (2.58)
t_{max} (h)	0.6[a] (0.3)	1.8 (1.7)	1.5 (1.1)	1.3[c] (0.6)	1.4 (1.4)	1.7 (1.3)
$AUC_{0-\tau}$ (µg·h/mL/200 mg Dose and 70 kg)	52.3 (17.2)	51.5 (15.3)	46.6 (9.4)	123.3[c] (35.8)	113.9 (33.3)	100.2 (23.3)
CL/F[d] (mL/min/70 kg))	69.8 (20.8)	69.2 (17.4)	74.1 (14.9)	29.5[c] (11.0)	31.7 (10.3)	35.1 (9.5)

[a] N = 4 for C_{max} and t_{max} - includes only q12h topiramate-treated subjects.
[b] Data from Subject 13 excluded from analysis as outlier data.
[c] N = 4 for C_{max} and t_{max} - includes only q12h topiramate-treated subjects. Subject 4 data excluded; subject received an additional dose.
[d] Weight-normalized, only.

Comparison to historical data from adult subjects with epilepsy indicated topiramate CL/F in pediatric subjects receiving topiramate adjunctive to enzyme inducing AEDs was 52% higher when compared to adult subjects (70.1 mL/min/70 kg - pediatric subjects vs 46.1 mL/min/70 kg - adult subjects). Pediatric subjects receiving topiramate adjunctive to nonenzyme inducing AEDs had a mean topiramate CL/F 48% higher compared to adult subjects (33.1 mL/min/70 kg - pediatric subjects vs 22.4 mL/min/70 kg -adult subjects). Consequently, steady-state plasma topiramate concentrations for the same mg/kg dose will be approximately 33% lower in pediatric patients compared to adults. A pronounced increase in weight-normalized blood CL/F with an associated decrease in dose- and weight-normalized blood C_{max} and $AUC_{0-\tau}$ with increasing dose was observed. This may be associated with saturable binding of topiramate to red blood cells. This is not expected to be of clinical consequence since the compartment more closely distributing topiramate to the site of action (brain) is the plasma.

SEIZURE COUNTS:

The median monthly seizure rate was 94.6 during the baseline phase and 55.0 during topiramate dosage titration. Because of the small sample size per age group, short baseline and treatment periods, and lack of a control group, a meaningful assessment of these results cannot be made.

SAFETY:

Treatment-Emergent Adverse Events

The most frequently reported treatment-emergent adverse events included abnormal thinking, anorexia, fatigue, injury, nervousness, and upper respiratory tract infection (URTI) (Table 5). The majority of the adverse events were of mild severity and considered by the investigator to be unlikely or possibly related to topiramate. No treatment-emergent adverse event was considered to be of marked severity or definitely related to topiramate.

Table 5: Incidence of the Most Common[a] Treatment-Emergent Adverse Events Summarized by Body System and Primary Term (All Subjects; Protocol TOPMAT-EPPD-001)

	Age (yr) Group			
	4-7 (N=6)	8-11 (N=6)	12-17 (N=6)	Total (N=18)
Body System/Primary term	No.	No.	No.	No. (%)
Psychiatric				
Anorexia	2	2	3	7 (39)
Nervousness	3	0	1	4 (22)
Thinking abnormal	1	1	4	6 (33)
Body as a Whole				
Fatigue	2	0	5	7 (39)
Injury	4	0	0	4 (22)
Respiratory System				
URTI	2	1	2	5 (28)

[a] Includes treatment-emergent adverse events occurring in at least 20% of the subjects in any age group.

Other Safety Assessments

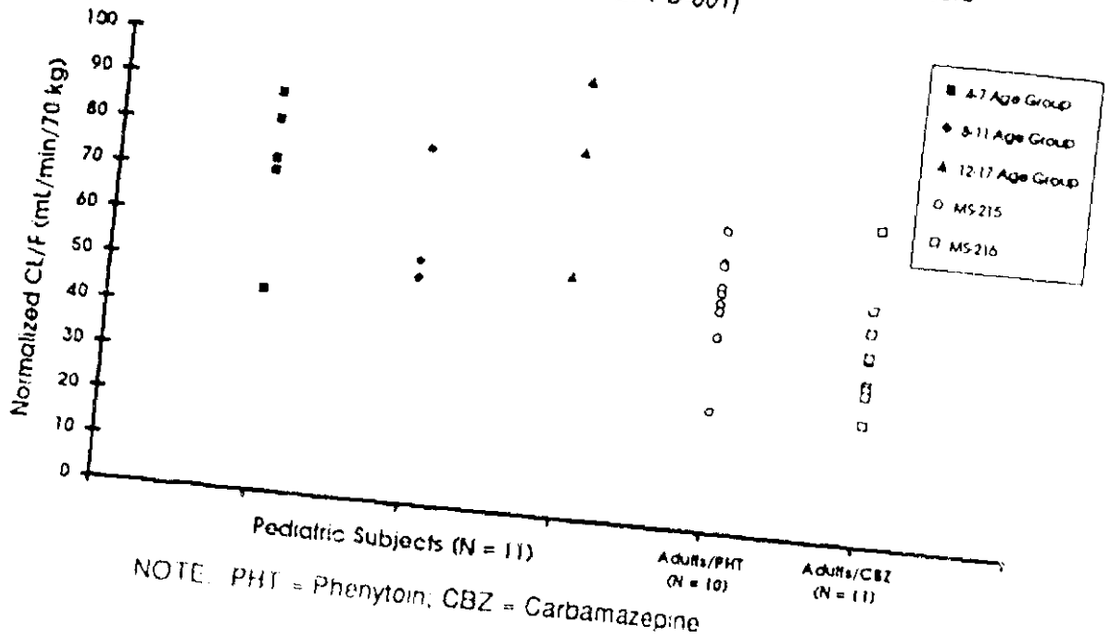
The mean changes from baseline for all clinical laboratory analyte or vital sign measurements were not of sufficient magnitude to cause concern. All of the clinical laboratory analyte or vital sign measurement marked abnormalities were considered to be of no clinical concern. No treatment-emergent changes were noted in neurologic or physical examination results.

CONCLUSIONS:

The results from this study indicate topiramate pharmacokinetics were linear in 4 to 17 year-old pediatric subjects. Topiramate plasma CL/F was independent of dose and steady-state plasma concentrations increased in proportion to dose. Topiramate CL/F was higher in subjects receiving enzyme inducing concomitant antiepileptic drugs when compared to subjects not receiving enzyme inducing concomitant antiepileptic drugs. Comparison to historical data from adult subjects with epilepsy indicates mean topiramate plasma CL/F in pediatric subjects receiving topiramate adjunctive to enzyme inducing or noninducing AEDs was approximately 50% higher than in adult subjects receiving the same type of concomitant AED. Consequently, steady state plasma topiramate concentrations for the same mg/kg dose will be approximately 33% lower in pediatric patients compared to adults. The results of this study support the safety and tolerability of topiramate in pediatric subjects with epilepsy.

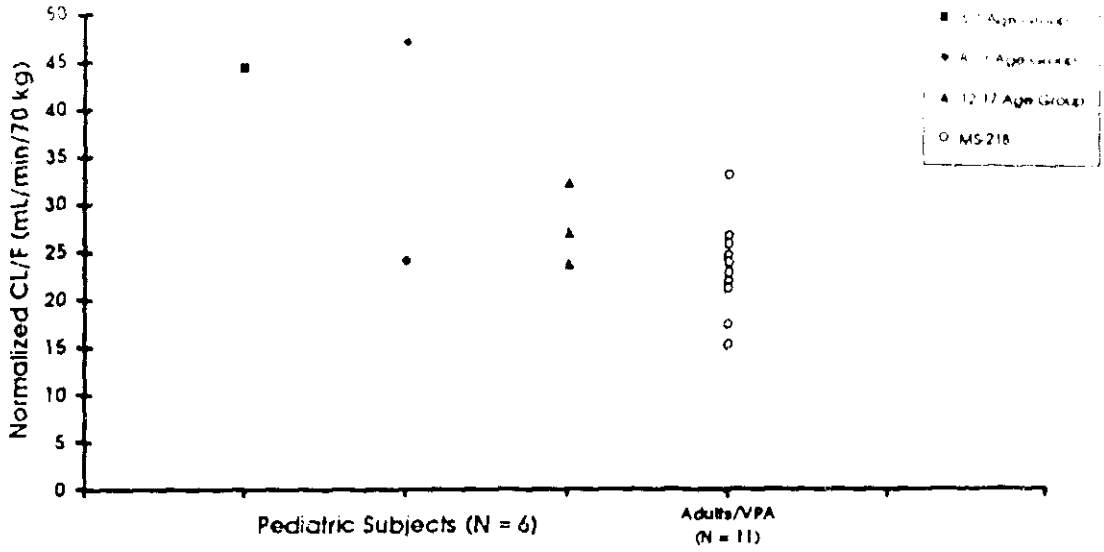
subjects (70.1 mL/min/70 kg - pediatric subjects vs 46.1 mL/min/70 kg - adult subjects). Pediatric subjects receiving topiramate adjunctive to non-enzyme-inducing AEDs had a mean topiramate CL/F 48% higher when compared to adult subjects (33.1 mL/min/70 kg - pediatric subjects vs 22.4 mL/min/70 kg - adult subjects).

Figure 2: Comparison of Mean Weight-Normalized CL/F from Pediatric and Adult Subjects With Epilepsy Receiving Topiramate With Concomitant Enzyme Inducers (Protocol TOPMAT-EPPD-001)



NOTE: PHT = Phenytoin; CBZ = Carbamazepine

Figure 3: Comparison of Mean Weight-Normalized CL/F from Pediatric and Adult Subjects With Epilepsy Receiving Topiramate Without Concomitant Enzyme Inducers (Protocol TOPMAT EPPD 001)



NOTE: VPA = Valproic acid

The pronounced increase in weight-normalized blood CL/F and associated decrease in dose- and weight-normalized blood C_{max} and $AUC_{0-\tau}$ with increasing dose may be associated with saturable binding of topiramate to red blood cells. This is not expected to be of clinical consequence since the compartment more closely distributing topiramate to the site of action (brain) is plasma.

The median monthly seizure rate was 94.6 during baseline and 55.0 during the topiramate treatment phase of this study. Because of the small sample size per age group, short baseline and treatment periods, and lack of a control group, a meaningful assessment of these results cannot be made.

The most frequently reported treatment-emergent adverse events included abnormal thinking, anorexia, fatigue, injury, nervousness, and upper respiratory tract infection. The majority of the adverse events were of mild

APPENDIX 2

DRUG METABOLISM
Department # DM92355

COMPARATIVE STEADY-STATE BIOAVAILABILITY OF NORETHINDRONE AND ETHINYL ESTRADIOL (ORTHO-NOVUM® 1/35□28) IN FEMALE PATIENTS WITH EPILEPSY ON VALPROIC ACID MONOTHERAPY BEFORE AND AFTER ADD-ON TOPAMAX™ TOPIRAMATE THERAPY (PROTOCOL DM92355)

SUMMARY

The objective of this study was to evaluate the potential pharmacokinetic interaction between topiramate and the oral contraceptive combination, norethindrone and ethinyl estradiol (ORTHO-NOVUM® 1/35□28) in 12 female patients with epilepsy. The patients were stabilized on valproic acid monotherapy. Valproic acid was selected because it has been demonstrated to have negligible pharmacokinetic interaction with steroid oral contraceptives. The study was designed to determine within the same group of female patients the steady-state pharmacokinetics of norethindrone and ethinyl estradiol while on a) valproic acid monotherapy, and b) combination valproic acid and topiramate therapy at each of three escalating topiramate doses. The patients were receiving 750-2500 mg/day valproic acid and their ages ranged from 20-39 years (mean, 27.7 years) and weight ranged from 100-164.5 pounds (mean, 142.4 pounds).

Only patients who were stabilized on a fixed dosage regimen of valproic acid monotherapy of equally divided doses administered q12h were entered into the study. Patients who were not currently on oral hormonal contraceptives entered the study during the fourth to sixth day of menses by starting daily morning dosing of the oral contraceptive. Patients already on ORTHO-NOVUM® 1/35□28 or another oral hormonal contraceptive (direct switch-over patients) entered the study by starting daily morning dosing of ORTHO-NOVUM® 1/35□28 without interruption on the day after the 7-day pill-free interval (21-day regimen) or the seven inactive pills (28-day regimen) of their previous oral contraceptive. Following the first 28-day cycle, patients resumed daily dosing of the oral contraceptive and started 100 mg h.s. topiramate therapy for 3 days, then 100 mg topiramate q12h for the remainder of the 28-day cycle. After the second 28-day cycle, patients resumed daily dosing of the oral contraceptive and started 200 mg h.s. and 100 mg q.a.m. topiramate therapy for 3 days followed by 200 mg q12h for the remainder of the 28-day cycle. After the third 28-day cycle, patients increased their daily topiramate dose to 400 mg h.s. and 200 mg q.a.m. for 3 days followed by 400 mg q12h for the remainder of the 28-day cycle.

Patients were sequestered at the investigator's facility from the evening of the 19th day of each of the four 28-day cycles until the 12 hour blood sample was obtained on the following day. Patients returned to the investigator's site in the morning of

Day 21 of each cycle to withdraw 24-hour postdosing sample. Topiramate, valproic acid and the oral contraceptive were administered on profiling Day 20 following a 12-hour overnight fast and on Day 21 before the 24-hour blood sample was obtained. Topiramate 100 mg tablets (Formula No. 37, Batch No. R4561), 200 mg tablets (Formula No. 47, Batch No. R4562), and 400 mg tablets (Formula No. 36, Batch No. R4563) were used in this study. ORTHO-NOVUM® 1/35□28 DIALPAK® tablets (Batch No. R4636, Lot No. 22L512) were used in this study. The investigator supplied Depakote® brand of valproic acid.

Blood samples were collected for 24 hours following the morning dose of valproic acid and oral contraceptive on Day 20 of Cycle 1 prior to initiation of topiramate dosing. Blood samples were collected for 24 hours following the morning dose of valproic acid, oral contraceptive and topiramate on Day 20 of Cycle 2 (100 mg q12h topiramate dosing), Cycle 3 (200 mg q12h topiramate dosing), and Cycle 4 (400 mg q12h topiramate dosing). An additional 24-hour blood sample was obtained during each cycle to determine progesterone levels to evaluate the occurrence of ovulation. Blood samples were processed for serum and analyzed for norethindrone and ethinyl estradiol, or progesterone by validated and specific radioimmunoassay methods.

Norethindrone Pharmacokinetics

Mean norethindrone steady-state serum pharmacokinetic parameters before add-on topiramate therapy and during concomitant topiramate dose escalation are presented in the following table.

Steady-State Serum Norethindrone Pharmacokinetic Parameters Before Topiramate Add-On Therapy and During Concomitant Topiramate Dose Escalations

Norethindrone Parameters		Concomitant Topiramate Dose				
		Cycle 1 None	Cycle 2 100 mg q12h	Cycle 3 200 mg q12h	Cycle 4 400 mg q12h	ANOVA[a,b]
C_{max} (ng/mL)	Mean (SD)	24.4 (8.9)	24.3 (9.2)	25.9 (9.9)	24.8 (13.0)	
	Range	8.4-36.1	8.6-44.8	8.7-42.6	7.7-48.8	NS
T_{max} (h)	Mean (SD)	1.6 (0.8)	1.2 (0.4)	1.5 (0.7)	1.7 (0.6)	NS
	Range	1.0-3.0	1.0-2.2	1.0-3.0	1.0-3.0	
AUC (0-24 h) (ng·h/mL)	Mean (SD)	235 (109)	222 (108)	226 (101)	218 (130)	NS
	Range	74-458	65-454	56-410	44-513	
CL/F (mL/min)	Mean (SD)	88.0 (49.1)	95.5 (57.6)	97.7 (7[illegible].9)	112.9 (95.4)	NS
	Range	36.4-223.9	36.7-255.5	40.7-296.7	32.5-382.3	
k_a (h^{-1})	Mean (SD)	0.0556 (0.0156)	0.0596 (0.0236)	0.0679 (0.0245)	0.0783 (0.0351)	NS
	Range	0.0343-0.0900	0.0335-0.1118	0.0408-(0.1136)	0.0304-0.1414	
$t_{1/2}$ (h)	Mean (SD)	13.3 (3.5)	13.0 (3.9)	11.3 (3.5)	10.7 (5.0)	NS
	Range	7.8-20.2	6.2-20.7	6.1-17.0	4.9-22.8	

[a] From ANOVA. NS = Not statistically significantly different ($p>0.05$)

[b] Van der Waerden scores were used for T_{max}

No significant differences in norethindrone pharmacokinetic parameters were observed in the presence of concomitant topiramate doses of 100 to 400 mg q12h compared to baseline parameters in the absence of topiramate.

Ethinyl Estradiol Pharmacokinetics

Mean ethinyl estradiol steady-state serum pharmacokinetic parameters before add-on topiramate therapy and during concomitant topiramate dose escalation are presented in the following table.

Steady State Serum Ethinyl Estradiol Pharmacokinetic Parameters Before Topiramate Add-On Therapy and During Concomitant Topiramate Dose Escalations

Ethinyl Estradiol Parameter		Concomitant Topiramate Dose					
		Cycle 1 None	Cycle 2 100 mg q12h	Cycle 3 200 mg q12h	Cycle 4 400 mg q12h	ANOVA[a,b]	Contrast with Cycle 1
Cmax (pg/mL)	Mean (SD)	248 (89)	211 (61)	204 (63)	185 (67)	SIG	Cycle 2 = Cycle 1 Cycle 3 < Cycle 1 Cycle 4 < Cycle 1
	Range	102-356	129-329	111-303	89.6-266		
Tmax (h)	Mean (SD)	1.2 (0.4)	1.4 (0.9)	1.3 (0.5)	1.7 (0.8)	NS	
	Range	1.0-2.0	0.9-4.0	1.0-2.0	1.0-3.0		
AUC (0-24 h) (pg·h/mL)	Mean (SD)	2232 (886)	1831 (602)	1762 (492)	1562 (510)	SIG	Cycle 2 < Cycle 1 Cycle 3 < Cycle 1 Cycle 4 < Cycle 1
	Range	1074-3650	1075-2926	955-2688	995-2514		
CL/F (mL/min)	Mean (SD)	306 (131)	351 (111)	360 (120)	407 (119)	SIG	Cycle 2 > Cycle 1 Cycle 3 = Cycle 1 Cycle 4 > Cycle 1
	Range	160-543	199-543	217-611	232-587		
k_e (h^{-1})	Mean (SD)	0.0582 (0.0444)	0.0490 (0.0156)	0.0491 (0.0182)	0.0422 (0.0175)	NS	
	Range	0.0270-0.1888	0.0237-0.0809	0.0262-0.0809	0.0302-0.0762		
$t_{1/2}$ (h)	Mean (SD)	15.7 (6.6)	15.7 (5.6)	16.2 (6.5)	19.3 (8.6)	NS	
	Range	3.7-25.6	8.6-29.2	8.6-27.7	9.1-38.0		

[a] From ANOVA NS = Not statistically significantly different
SIG = Statistically significantly different ($p \leq 0.05$)
[b] Van der Waerden scores were used for T_{max}

Concomitant topiramate therapy resulted in a decrease in serum C_{max} and AUC values and an increase in oral serum clearance values of ethinyl estradiol compared to corresponding values in the absence of topiramate. There was a trend toward greater decreases in mean C_{max} and AUC values and greater increases in mean CL/F values with escalating topiramate doses. Contrasts with Cycle 1 showed that differences between mean parameter values achieved statistical significance for Cycles 3 and 4 for C_{max}, Cycles 2 to 4 for AUC, and Cycles 2 and 4 for CL/F. The mean C_{max} and AUC values decreased a maximum of 25.3% and 30.0%, and the mean CL/F increased a maximum of 32.9% at the highest topiramate dose (Cycle 4). The T_{max} of ethinyl estradiol was not affected by topiramate.

Mean serum ethinyl estradiol $t_{1/2}$ and k_e values were not statistically significantly different among contrasts with Cycle 1. However, there was a slight trend toward an increase in $t_{1/2}$ (decrease in k_e) with escalating topiramate doses.

Progesterone Concentrations

Serum progesterone concentrations from cycle Day 21 before add-on topiramate therapy and during concomitant topiramate dose escalation for all patients were close to or at the limit of quantification. No apparent differences were observed among cycles.

The results from this study show that therapeutic topiramate dosing regimes have no effect on norethindrone pharmacokinetics, but reduce mean ethinyl estradiol plasma concentrations by as much as 30%. Since no effect on the progestin component was observed and only a maximum mean 30% reduction in ethinyl estradiol concentrations occurred, which would give similar ethinyl estradiol concentrations as seen with a 20 µg ethinyl estradiol dose (known to be effective), there is likely to be no clinically significant effect on the contraceptive efficacy of ORTHO-NOVUM® 1/35□28 by concomitant administration of topiramate. This is supported by the progesterone serum concentration results determined on Day 21 of each cycle during this study. During the preovulatory phase progesterone concentration is less than 1 ng/mL. If ovulation occurs, progesterone levels begin to rise at the time of the luteinizing hormone surge (approximately Day 14 of the menstrual cycle) and reach a peak of about 10-20 ng/mL 4 to 6 days postovulation (approximately Days 20-22 of the menstrual cycle). All Day 21 progesterone concentrations determined in this study were less than 0.005 ng/mL, suggesting that no ovulation occurred within the 4 to 6 day window around Day 21, and ORTHO-NOVUM® 1/35□28 effectively prevented ovulation in the study patients prior to and after addition of topiramate therapy within this time window. There is, however, a possibility that patients ovulated outside of the Day 15 to 27 window, in which case it would not have been detected.

The selective reduction of only the estrogen serum concentrations may result in an increase in breakthrough bleeding for the patient. It is recommended that patients starting concomitant oral contraceptives and topiramate be prescribed an oral contraceptive that contains a 50 µg dose of the estrogen component. If the patient has no breakthrough bleeding on a 50 µg ethinyl estradiol dose oral contraceptive, a lower dose ethinyl estradiol oral contraceptive may be considered

However, if breakthrough bleeding on the lower dose occurs while taking topiramate, this may indicate inadequate ovulation suppression and the physician should consider increasing the ethinyl estradiol dose in the oral contraceptive

NOTEBOOK REFERENCES:

RWJPRI Drug Metabolism Project Notebook for DM92355.

Figure 1 Mean Steady-State Norethindrone Serum Concentrations

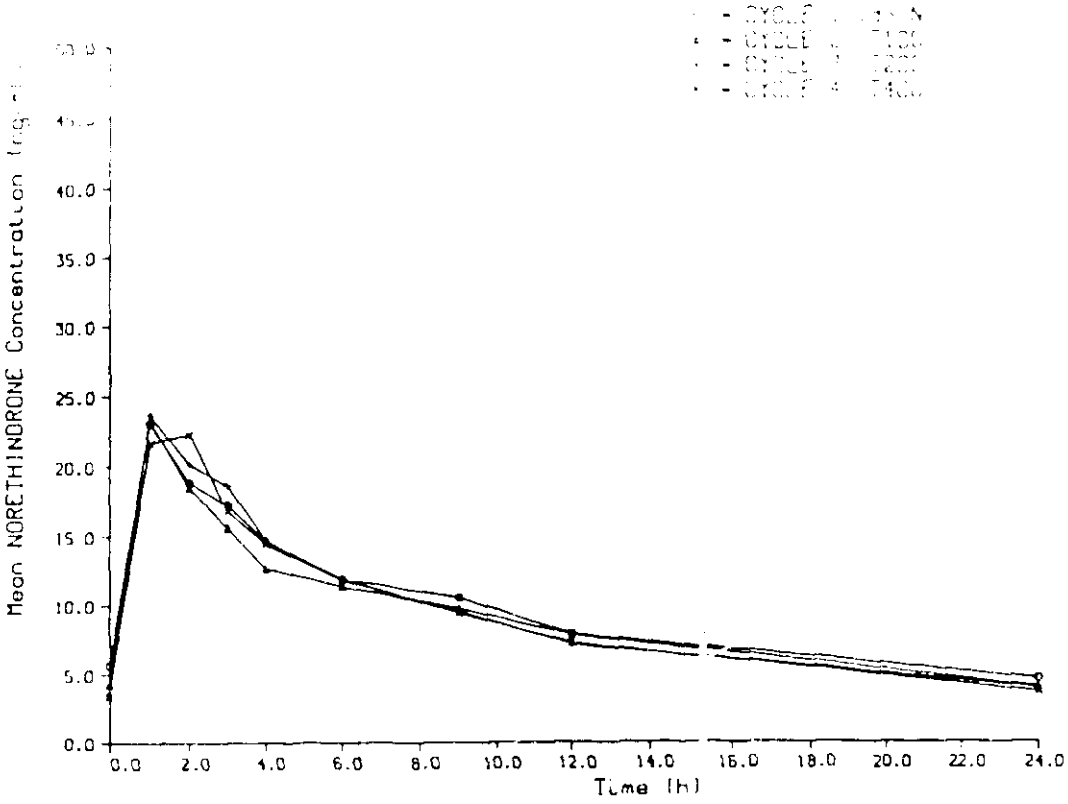
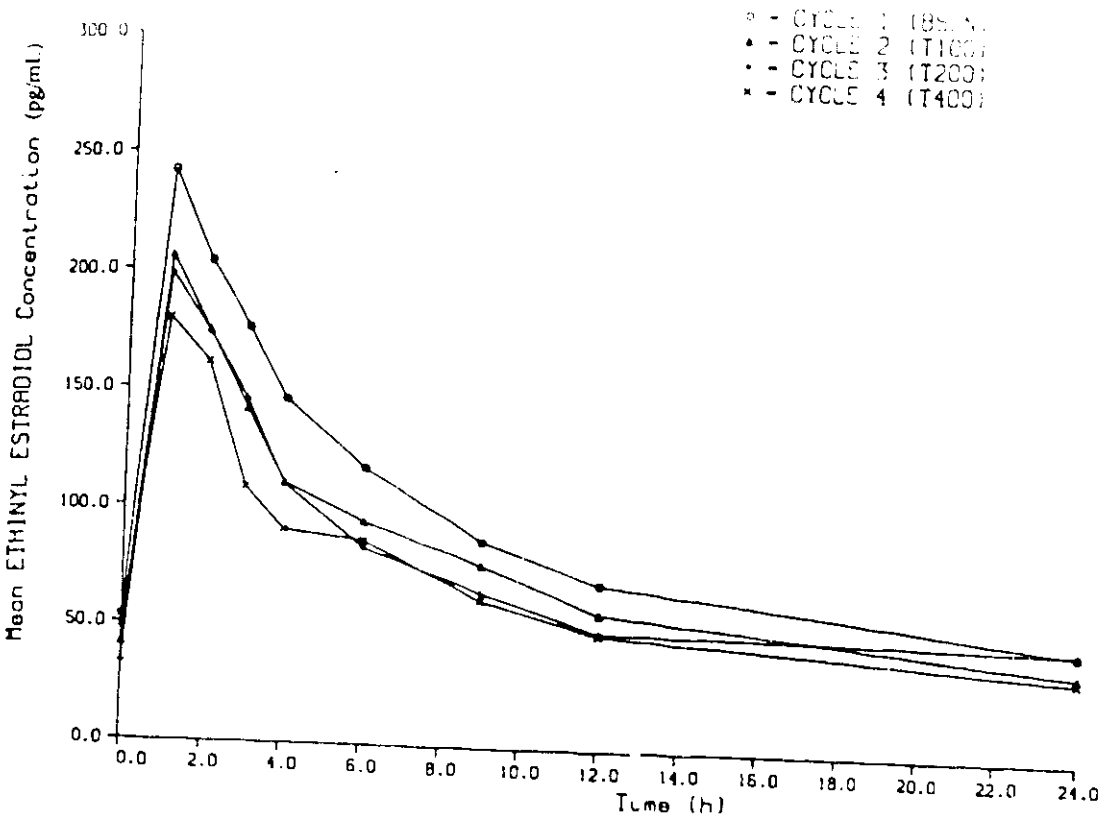


Figure 2: Mean Steady-State Ethinyl Estradiol Serum Concentration



Ethinyl estradiol concentrations at 0 hour and 24 hours indicated a steady-state had been achieved by sampling Day 20 for each cycle. Mean (±SD) steady-state pharmacokinetic parameters for ethinyl estradiol in absence of topiramate and with concomitant topiramate dose therapy are shown in Table 3.